(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 024 096**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 80301723.5

(22) Date of filing: 23.05.80

(51) Int. Cl.³: C 07 F 1/08
C 07 C 147/14, C 07 C 103/36
C 07 C 65/00, C 07 C 101/52
C 07 C 149/20, C 07 C 163/00
A 61 K 31/30, A 61 K 31/60

(30) Priority: 15.08.79 AU 41 79

(43) Date of publication of application:
25.02.81 Bulletin 81/8

(84) Designated Contracting States:
BE CH DE FR GB LI LU NL SE

(71) Applicant: Boettcher, Barry
12 Mahogany Drive
New Lambton New South Wales, 2305(AU)

(71) Applicant: Walker, William Raymond
University of Newcastle
New South Wales, 2308(AU)

(71) Applicant: Whitehouse, Michael Wellesley
Department of Experimental Pathology Australian
National University
Canberra A.C.T., 2600(AU)

(72) Inventor: Boettcher, Barry
12 Mahogany Drive
New Lambton New South Wales, 2305(AU)

(72) Inventor: Walker, William Raymond
University of Newcastle
New South Wales, 2308(AU)

(72) Inventor: Whitehouse, Michael Wellesley
Department of Experimental Pathology Australian
National University
Canberra A.C.T., 2600(AU)

(74) Representative: Burnside, Michael et al,
c/o Michael Burnside & Partners 2 Serjeants' Inn Fleet
Street
London EC4Y 1HL(GB)

(54) Complexes of bivalent copper, methods of preparation thereof and compositions containing said complexes.

(57) Neutral copper complexes, particularly copper salicylate complexes having the formula $Cu[C_6H_4(OH)COO]_2 \cdot \gamma$ in which γ is dimethyl sulphoxide or dimethylformamide, have been found to have therapeutic activity in the treatment of inflammatory diseases and copper deficiency conditions. The complexes have been found particularly suitable for the treatment of Menkes' syndrome.

EP 0 024 096 A2

Croydon Printing Company Ltd.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 024 096**
A2

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 80301723.5

(22) Date of filing: 23.05.80

(51) Int.Cl.³: C 07 F 1/08
C 07 C 147/14, C 07 C 103/36
C 07 C 65/00, C 07 C 101/52
C 07 C 149/20, C 07 C 163/00
A 61 K 31/30, A 61 K 31/60

(30) Priority: 15.08.79 AU 4179

(43) Date of publication of application:
25.02.81 Bulletin 81/8

(84) Designated Contracting States:
BE CH DE FR GB LI LU NL SE

(71) Applicant: Boettcher, Barry
12 Mahogany Drive
New Lambton New South Wales, 2305(AU)

(71) Applicant: Walker, William Raymond
University of Newcastle
New South Wales, 2308(AU)

(71) Applicant: Whitehouse, Michael Wellesley
Department of Experimental Pathology Australian
National University
Canberra A.C.T., 2600(AU)

(72) Inventor: Boettcher, Barry
12 Mahogany Drive
New Lambton New South Wales, 2305(AU)

(72) Inventor: Walker, William Raymond
University of Newcastle
New South Wales, 2308(AU)

(72) Inventor: Whitehouse, Michael Wellesley
Department of Experimental Pathology Australian
National University
Canberra A.C.T., 2600(AU)

(74) Representative: Burnside, Michael et al,
c/o Michael Burnside & Partners 2 Serjeants' Inn Fleet
Street
London EC4Y 1HL(GB)

(54) **Complexes of bivalent copper, methods of preparation thereof and compositions containing said complexes.**

(57) Neutral copper complexes, particularly copper salicylate complexes having the formula $Cu[C_6H_4(OH)COO]_2\gamma$ in which γ is dimethyl sulphoxide or dimethylformamide, have been found to have therapeutic activity in the treatment of inflammatory diseases and copper deficiency conditions. The complexes have been found particularly suitable for the treatment of Menkes' syndrome.

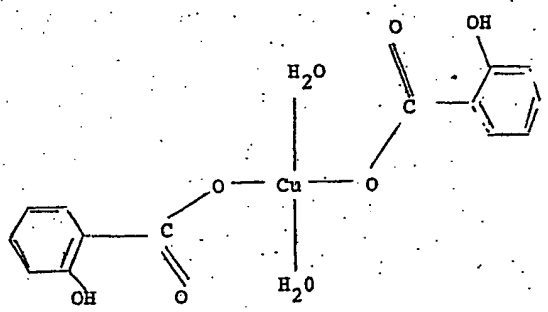
EP 0 024 096 A2

"COMPLEXES OF BIVALENT COPPER, METHODS OF PREPARATION THEREOF AND COMPOSITIONS CONTAINING SAID COMPLEXES"

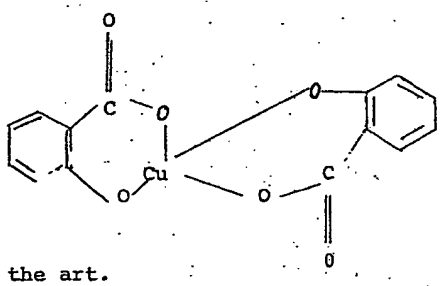
This invention relates to novel anti-inflammatory copper complexes and to anti-inflammatory compositions and processes utilizing such complexes.

Many studies of the role of copper, and especially complexes of copper, in the treatment of inflammatory diseases have been reported in recent years. One of the most recent studies describes the use of parenterally administered copper complexes, and particularly copper (II) salicylate, in the treatment of rheumatic disease (Sorenson and Hangarter, Inflammation, 2, 217-238 (1977)).

The prior art describes a wide variety of copper-salicylate complexes prepared by the reaction of inorganic copper (II) salts with salicylic acid in aqueous solution. The specific complex formed in aqueous solution has been found to depend on the pH of the aqueous solution and both neutral complexes such as the pale blue crystalline bis (salicylato) copper (II) tetrahydrate



and anionic complexes such as the olive green sodium salicylatocuprate (II)

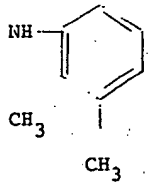


are known in the art.

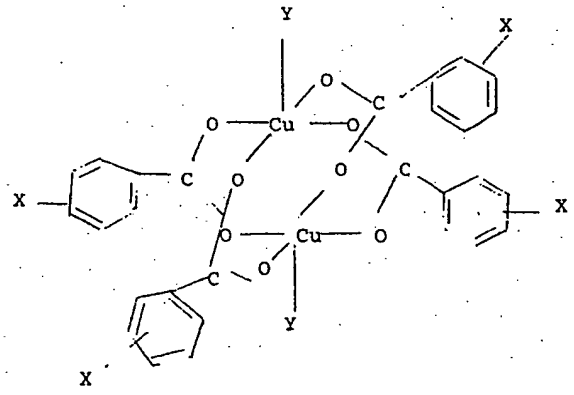
In our prior European patent application no. 78300671.1 filed on November 27, 1978, we described the use of copper complexes prepared by the reaction of copper compounds and substituted benzoic acids in the presence of an alkanol.

It is an object of this invention to provide novel neutral copper complexes prepared by the reaction of copper compounds and substituted benzoic acids in the presence of dimethylsulphoxide or dimethylformamide. A further object of the invention is to provide a method for the treatment of inflammatory diseases of animals by the administration of compositions comprising as active ingredient the novel copper complexes of the invention.

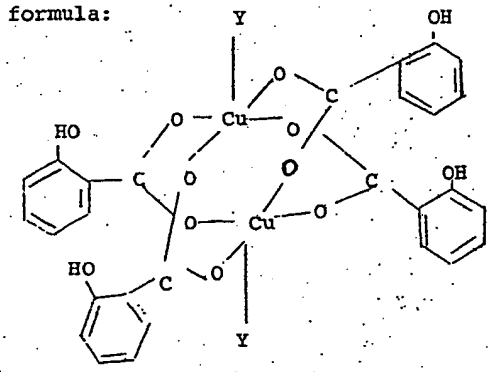
Accordingly in one embodiment the invention provides neutral copper complexes of the formula $Cu[C_6H_4(X)COO]_2 Y$ wherein Y represents dimethylsulphoxide or dimethylformamide, and wherein X can be located in any position and is OH, SH, SeH, NH_2 or



Although in no way wishing to be bound by theory, as a result of physico-chemical studies the complexes of the invention are believed to have the following dimeric structure:



The preferred compound according to the invention is the copper salicylate complex which is believed to have the formula:



The compounds of the invention may be prepared by reacting inorganic copper (II) compounds, for example copper salts or cupric hydroxide, with the appropriate substituted benzoic acid in the presence of dimethylsulphoxide or dimethylformamide. For example, reaction of cupric hydroxide with salicylic acid and dimethylsulphoxide gives the complex of formula $Cu[C_6H_4(OH)COO]_2.(CH_3)_2SO$, hereinafter referred to by the formula Cu[H Sal]$_2$. D.M.S.O., which forms fine deep green crystals when crystallised from anhydrous dimethylsulphoxide containing excess (approx. 5M) salicylic acid.

The compounds of the invention have been found to be particularly useful in the treatment of inflammatory diseases in animals. Thus in a further embodiment the invention provides a process for the treatment of inflammatory diseases of animals which process comprises administering to said animals an effective amount of a compound of the invention as hereinbefore defined.

The compounds of the invention have proved particularly effective in alleviating the symptoms of inflammatory diseases such as rheumatic disease.

arthritis and rheumatoid arthritis when applied topically to the animal.

Preferably the compounds of the invention are applied in the form of a composition comprising a compound of the invention in admixture with a pharmaceutically acceptable carrier. Therefore, in yet a further aspect the invention provides pharmaceutical anti-inflammatory compositions comprising a compound of the invention as hereinbefore defined and a pharmaceutically acceptable carrier therefor. The carrier preferably comprises an excess of the dimethylsulphoxide or dimethylformamide and an emollient such as glycerol.

Preferably the composition also contains a buffer for increasing the pH to prevent irritation by the salicylic acid; such buffers may include, for example, sodium acetate.

The compositions are preferably suitable for topical application to animals to be treated and therefore may be in the form of a gel, an ointment, a paste, a cream or a lotion. Compositions comprising a compound of the invention in solution are preferred as they are more efficient in perfusing the skin.

The amount of the compound of the invention employed in the compositions will depend to a large extent on the inflammatory condition being treated. However, as a general rule the compositions may comprise from 0.1 to 15% w/v of the copper compounds of the invention and preferably from 1 to 7% w/v.

As previously indicated the compounds of the invention have proved particularly useful in the alleviation of the symptoms of inflammatory disease when applied topically to the animal in the form of a pharmaceutical composition as hereinbefore defined. The compounds are believed to be efficacious in such

treatments because of their ready penetration of the skin. Furthermore, the compounds are believed to offer particular advantages in the treatment of inflammatory diseases of humans because of the non-toxic nature of the compounds and evidence that the compounds are readily cleared from the treated animal as indicated by the limited duration of the anti-inflammatory effect of the compounds.

The compositions may comprise, in addition to one or more compounds of the invention, other pharmaceutically active ingredients including other anti-inflammatory agents and conventional pharmaceutical excipients known in the art.

The invention is now illustrated by but not limited to the following examples.

EXAMPLE 1

Preparation of $Cu[C_6H_4(OH)COO]_2 \cdot (CH_3)_2SO$

Cupric hydroxide (1.0g) and salicylic acid (5.0g) were dissolved in dimethylsulphoxide (10 ml) and heated on a water bath. The solution was refrigerated for 48 hours. Fine deep-green crystals were deposited, filtered off, washed with benzene and dried over P_2O_5 under vacuum.

Yield 0.5 g (Found: Cu, 15.5; C, 45.9; H, 4.0; S7.8; $CuC_{16}H_{16}O_7S$ requires Cu, 15.4; C, 46.1; H, 4.3; S78%)

EXAMPLE 2

Preparation of $Cu[C_6H_4(OH)COO]_2 \cdot C_3H_7NO$

Cupric hydroxide (1.0 g) and salicylic acid (5.0 g) were dissolved in N,N-dimethylformamide (12 ml) and heated on a hot water bath. After refrigerating the resultant solution for 24 hours, green crystals were deposited. These were filtered off, washed with benzene and dried over P_2O_5 under vacuum. Yield 0.43 g.

(Found: Cu 15.4; C 49.6; H 4.1; N 3.3% $CuC_{17}H_{17}O_7N$ requires Cu 15.5; C 49.7; H 4.2; N 3.4%)

The products of the invention are rapidly absorbed through the skin and are promising materials for the treatment of copper deficiency conditions, for example Menkes' syndrome in which copper cannot be metabolised from the gut, leading to mental retardation, albinism and central nervous system disorders.

The absorption of topically applied products of the invention is illustrated in the following example.

EXAMPLE 3

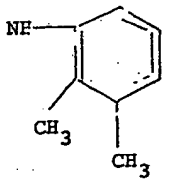
3.0 ml of a preparation comprising 1g $Cu(OH)_2$ 7 g salicylic acid 80 ml ethanol 20 ml glycerol, was rubbed on a human forearm and the concentration of salicylic acid measured in the serum. For comparison, the same concentrations of salicylic acid in same vehicle was used. High pressure liquid chromatography was used for analysis.

	Conc^n. Test Preparation	H_2sal* Vehicle
Time after application 2h	0.4	0.7
4h	1.7	1.3
6h	1.3	0.8

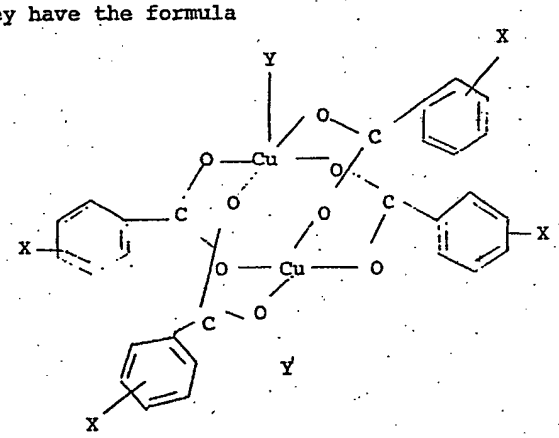
*µg/ml serum

CLAIMS:

1. Neutral copper complexes characterized in that they have the formula $Cu[C_6H_4(X)\ COO]_2\ Y$ wherein Y represents dimethylsulphoxide or dimethyl formamide, and wherein X can be located in any position and is OH, SH, SeH, NH_2 or

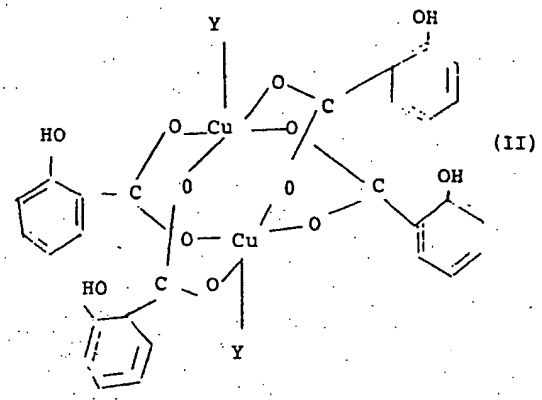


2. Complexes according to claim 1 characterized in that they have the formula



3. Complexes according to claim 1 or claim 2, characterized in that X is OH.

4. Complexes according to claim 2 characterized in that they have the formula



(II)

5. A method of preparing complexes as claimed in any of claims 1 to 4 characterized in that it comprises reacting an inorganic copper (II) compound with a substituted benzoic acid in the presence of dimethylsulphoxide or dimethylformamide.

6. A method according to claim 5 characterized in that the substituted benzoic acid is salicylic acid.

7. A method according to claim 5 or claim 6, characterized in that the copper (II) compound is a salt or cupric hydroxide.

8. A pharmaceutical composition characterized in that it comprises a compound according to any one of claims 1 to 4 and a pharmaceutically acceptable carrier.

9. A composition according to claim 8, characterized in that the pharmaceutically acceptable carrier is a non-aqueous carrier.

10. A composition according to claim 10, characterized in that the carrier comprises dimethylsulphoxide or dimethylformamide; glycerol; and salicylic acid.

11. A composition according to any one of claims 8 to 10 which contains a buffer, for example sodium acetate

12. A composition according to any one of claims 8 to 11 characterized in that it contains 0.1 to 15% w/v, preferably 1 - 7% w/v, of active ingredient.

13. A method of treating inflammatory diseases characterized in that it comprises administering to the patient an effective amount of a composition as claimed in any one of claims 1 to 4 and 8 to 12.